BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/00, A23G 3/30 — A1

(11) International Publication Number: **WO 97/21424**

(43) International Publication Date: 19 June 1997 (19.06.97)

(21) International Application Number: PCT/EP96/05468

(22) International Filing Date: 6 December 1996 (06.12.96)

(30) Priority Data:
9525240.9 9 December 1995 (09.12.95) GB

(71) Applicant *(for all designated States except US)*: LABORATOIRE GLAXO WELLCOME [FR/FR]; 43, rue Vineuse, F-75116 Paris (FR).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BOUAFFRE, Frédérique, Annie, Nathalie [FR/FR]; Laboratoire Glaxo Wellcome, Zone Industrielle No. 2, 23, rue Lavoisier, Boîte postale 3531, F-27035 Evreux Cédex (FR). LAFON, Jean-Pierre [FR/FR]; Laboratoire Glaxo Wellcome, Zone Industrielle No. 2, 23, rue Lavoisier, Boîte postale 3531, F-27035 Evreux Cédex (FR). PERRIN, Jean, Laurent, André [FR/FR]; Laboratoire Glaxo Wellcome, Zone Industrielle No. 2, 23, rue Lavoisier, Boîte postale 3531, F-27035 Evreux Cédex (FR). SALANÇON, Xavier, Marc [FR/FR]; Laboratoire Glaxo Wellcome, Zone Industrielle No. 2, 23, rue Lavoisier, Boîte postale 3531, F-27035 Evreux Cédex (FR).

(74) Agent: VOLCKMAN, Janis, Florence; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: CHEWING GUM CONTAINING RANITIDINE

(57) Abstract

The present invention provides a chewing gum composition comprising a gum base, a non-hygroscopic bulking agent, a flavouring, a high-intensity sweetener and ranitidine, or a physiologically acceptable salt thereof and a process for its preparation.

5519
10
25
70
150
156
452
469
504
551-555
556
558
574
799
810

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgystan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic			SE	Sweden
CG	Congo	KR	Republic of Korea	SG	Singapore
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LR	Liberia	SZ	Swaziland
CS	Czechoslovakia	LT	Lithuania	TD	Chad
CZ	Czech Republic	LU	Luxembourg	TG	Togo
DE	Germany	LV	Latvia	TJ	Tajikistan
DK	Denmark	MC	Monaco	TT	Trinidad and Tobago
EE	Estonia	MD	Republic of Moldova	UA	Ukraine
ES	Spain	MG	Madagascar	UG	Uganda
FI	Finland	ML	Mali	US	United States of America
FR	France	MN	Mongolia	UZ	Uzbekistan
GA	Gabon	MR	Mauritania	VN	Viet Nam

CHEWING GUM CONTAINING RANITIDINE.

The present invention relates to improvements in the formulation of the histamine H_2-receptor antagonist ranitidine, particularly for oral administration.

Ranitidine, N-[2-[[[5-(dimethylamino)methyl-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine, and its physiologically acceptable salts are described and claimed in British Patent Specification No. 1565966, and a particular crystalline form of ranitidine hydrochloride is described and claimed in British Patent Specification No. 2084580. In both these specifications there is reference to formulations for oral administration, which may take the form of for example tablets, capsules, granules, powders, solutions, syrups, suspensions, or tablets or lozenges for buccal administration.

Oral administration constitutes a preferred route for administering ranitidine. Ranitidine, however, in common with many drug substances, has an inherently bitter taste, and this constitutes a disadvantage with certain types of oral preparation. The problems resulting from the bitter taste of ranitidine are particularly acute in chewable formulations.

Chewing gum compositions for the oral, systemic delivery of H_2 antagonists have not previously been described, although topical chewing gum compositions for the treatment of gingivitis or periodontitis containing H_2-receptor antagonists are described generally in US5294433. Thus, compositions comprising 0.1% to 10% of an H_2 antagonist and a chewing gum carrier (comprising a gum base, a flavouring agent and a sweetening agent) are disclosed. There is no further teaching as to the nature of the chewing gum carrier, however, and chewing gum compositions containing ranitidine are not specifically disclosed.

Chewable formulations are a particularly convenient form of oral presentation for patients who prefer not to take swallowable tablets, or find difficulty in swallowing them. A chewing gum formulation would be a particularly convenient way of administering ranitidine systemically, especially in the treatment of minor conditions such as acid indigestion and heartburn. However, since chewing gums remain in the mouth for an extended period, such a formulation presents particular difficulties if the taste of ranitidine is to be effectively masked

A further problem to be overcome if one is to arrive at a sufficiently stable ranitidine chewing gum is due to ranitidine's tendency to degrade in the presence of moisture. Conventional sugar-free chewing gum compositions contain large amounts of hygroscopic sugar alcohols which result in the gum having a high moisture content, around 3 to 5%, which is further increased by moisture uptake on storage.

An additional problem with conventional chewing gums lies in the method used to prepare them. This involves mixing a heated chewing gum base with an aqueous solution of the sugar alcohol.

Substantially anhydrous chewing gum compositions have been described, for example US3262784 relates to dry, granular chewing gum compositions comprising a chewing gum base and sugar granules which produces chewing gum granules which can be compressed into shape.

US4961935 describes anhydrous chewing gum compositions comprising a gum base, a non-hygroscopic bulking agent, such as an isomalt, a softening agent and a sweetening agent. The chewing gum is prepared by heating the gum base at 60 to 120°C until molten, mixing with the other ingredients whilst still in the molten state and then forming the gum into shapes.

Thus, according to the method of US4961935, the chewing gum ingredients are exposed to a period of working at elevated temperature which could result in degradation of heat-sensitive components. Since it is known that the degradation of ranitidine is accelerated by heat, it would be advantageous to avoid excess exposure to heat during the formulation process.

A ranitidine chewing gum composition has now been discovered which avoids the problems of exposure to moisture and heat, thus ensuring the stability of ranitidine, and where the bitter taste of ranitidine is effectively masked and which provides a rapid and effective release of ranitidine resulting in advantageous bioavailability.

Thus, the present invention provides a chewing gum composition comprising a gum base, a non-hygroscopic bulking agent, a flavouring, a high-intensity sweetener and ranitidine, or a physiologically acceptable salt thereof.

Ranitidine may be employed in the compositions according to the invention in the form of either its free base or a physiologically acceptable salt. Such salts include salts with inorganic or organic acids such as the hydrochloride, hydrobromide, sulphate, acetate, maleate, succinate, citrate, tartrate, fumarate and ascorbate salts. A particularly preferred salt of ranitidine is the hydrochloride.

The gum base may be selected from any suitable water-insoluble gum base known in the art and includes those gum bases utilised for chewing gums and bubble gums. Thus, for example, the gum base may comprise a polymer, such as an elastomeric polymer, resins, waxes, glycerol esters of edible fatty acids, plasticizers, mineral adjuvants such as talc, and other conventional additives such as antioxidants. A particularly suitable gum base is the commercially available "DELTA T".

The gum base suitably comprises 15 to 20% of the total composition, for example around 18%. The ratio of gum base to non-hygroscopic bulking agent is suitably in the range 1:3 to 1:5, for example 1:4.

The non-hygroscopic bulking agent is preferably an isomalt, i.e. a mixture, such as a racemic mixture of 1-O-alpha-D-glucopyranosyl-D-mannitol and 6-O-alpha-D-glucopyranosyl-D-glucitol, for example the commercially available "PALATINIT" or "PALATINOL". The non-hygroscopic bulking agent suitably comprises 60 to 80% of the total composition, for example around 70%

The flavouring in the compositions according to the invention is a strong flavouring such as fruit flavours and natural or synthetic mint or peppermint flavours. Strong mint or peppermint flavourings are preferred.

The chewing gum composition also optionally contains an acidifiant agent such as sodium citrate.

The high intensity sweetener includes saccharine and cyclamic acid and their various salts or, more preferably, dipeptide sweeteners such as aspartame.

The chewing gum composition may also include a lubricant such as magnesium stearate.

Thus, in a preferred aspect, the present invention provides a chewing gum composition comprising a gum base, a non-hygroscopic bulking agent, e.g. an isomalt, a flavouring, e.g. a strong mint or peppermint flavouring, a high intensity sweetener, e.g. aspartame, a lubricant, e.g. magnesium stearate and ranitidine, or a physiologically acceptable salt thereof, e.g. the hydrochloride salt.

It will be appreciated that the chewing gum compositions according to the invention are for the oral, systemic delivery of ranitidine and not topical delivery. It will also be appreciated that the instant chewing gum compositions are essentially sugarless.

The chewing gum compositions according to the instant invention are preferably in the form of chewing gum tablets.

The amount of ranitidine, preferably in the form of a physiologically acceptable salt, particularly ranitidine hydrochloride, in the composition according to the invention is preferably in the range of 10 to 800mg per dosage unit (for example per chewing gum tablet), e.g. 20 to 600mg, more preferably 25 to 300mg, such as 25, 75, 125 or 150mg, expressed as the weight of free base.

The unit dose (for example contained in one chewing gum tablet according to the invention) may be administered up to, for example, 6 times a day depending upon the unit dose used, the nature and severity of the conditions being treated, and the age and weight of the patient. Thus, for example, in the treatment of minor conditions where there is an advantage in lowering gastric acidity such as, for example, acid indigestion, over-indulgence of food or drink, acid stomach, sour stomach, waterbrash/regurgitation, heartburn, such as episodic heartburn, nocturnal heartburn, and meal-induced heartburn, gastritis and dyspepsia, lower and more frequent doses of ranitidine may be used, for example doses in the range of 10-150mg, e.g. 25-75mg ranitidine expressed as the weight of free base, administered up to 6 times a day as and when required. For more serious conditions such as duodenal and gastric ulceration, reflux oesophagitis and Zollinger-Ellison syndrome, higher and less frequent doses of ranitidine will be employed, for example 75-600mg. e.g. 150mg unit doses administered one to four, preferably once or twice, daily.

The chewing gum compositions according to the instant invention may be prepared by heating the gum base until molten according to conventional

procedures, for example at around 70°C, allowing the gum base to cool, yet maintaining it in its molten state, for example at around 40-45°C, adding the preheated bulking agent, for example portion wise, e.g. 60% of the total amount, and at a temperature of, for example 30-35°C, and blending and cooling the mixture, for example at about 30°C. The remaining bulking agent is added, for example the remaining 40%, and the mixture is further blended and cooled, for example at around 25°C, at which stage a free flowing powder is produced.

The step of cooling and blending the gum base/bulking agent mixture to produce a free flowing powder is novel and constitutes a further aspect of the invention.

The free flowing powder is then blended with the ranitidine and other ingredients according to conventional anhydrous blending procedures. Thus, for example the gum base/bulking agent mixture is dry blended or dry granulated with ranitidine followed by the remaining ingredients and then the mixture is compressed into tablet shapes.

The following table illustrates non-limiting examples of the pharmaceutical compositions according to the invention.

In the following examples the gum base used is DELTA T, available from Cafosa Gum SA, Barcelona, Spain, and the isomalt is PALATINIT. DELTA T and PALATINIT are tradenames.

Ingredient	Example 1 mg/tablet	Example 2 mg/tablet	Example 3 mg/tablet	Example 4 mg/tablet
Ranitidine HCl	28.0	84.0	84.0	168.0
Gum Base	534	534	534	575
Isomalt	2100	2136	2136	2140
Peppermint Flavour	150	150	150	200
Sodium Citrate	-	-	30	30
Aspartame	10	22	22	25
Magnesium Stearate	40	44	44	60

CLAIMS

1. A chewing gum comprising a gum base, a non-hygroscopic bulking agent, a flavouring, a high-intensity sweetener and ranitidine, or a physiologically acceptable salt thereof.

2. A chewing gum according to claim 1 wherein the gum base comprises 15 to 20% of the total composition.

3. A chewing gum according to claim 1 or claim 2 wherein the non-hygroscopic bulking agent comprises 60 to 80% of the total composition.

4. A chewing gum according to any of claims 1 to 3 wherein the ratio of gum base to non-hygroscopic bulking agent is in the range 1:3 to 1:5.

5. A chewing gum according to any of claims 1 to 4 wherein the non-hygroscopic bulking agent is an isomalt.

6. A chewing gum according to claim 5 wherein the isomalt is a mixture of 1-O-alpha-D-glucopyranosyl-D-mannitol and 6-O-alpha-D-glucopyranosyl-D-glucitol.

7. A chewing gum according to any of claims 1 to 6 containing ranitidine hydrochloride.

8. A chewing gum according to any of claims 1 to 7 containing 25 to 300mg ranitidine, expressed as the weight of free base, per dosage unit.

9. A chewing gum according to any of claims 1 to 8 in the form of a chewing gum tablet.

10. A process for the preparation of a ranitidine chewing gum composition as defined in claim 1 which comprises cooling and blending a mixture of the gum base and bulking agent to produce a free flowing powder and blending with the ranitidine and other ingredients.

INTERNATIONAL SEARCH REPORT

Inter onal Application No
PC1/EP 96/05468

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/00 A23G3/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K A23G

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 294 433 A (SINGER ET AL.) 15 March 1994 cited in the application	1,8,9
Y	see column 20, line 33 - line 43; claims 1-4	10

X	CA 2 068 366 A (FAULDING (F.H.) & CO. LTD AUSTRALIA) 11 November 1992 see page 8, line 1 - line 20; claim 28	1

Y	DATABASE WPI Week 6800 Derwent Publications Ltd., London, GB; AN 66-15950f XP002028473 & JP 40 003 463 B (TAISHO PHARM. CO. LTD.) , 1968 see abstract	10

	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 March 1997	11. 04. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Lepretre, F

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 96/05468

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DE 28 08 160 A (NORDSTRÖM) 30 August 1979 see claims 1-3	10
Y	EP 0 151 344 A (WARNER LAMBERT COMPANY) 14 August 1985 see page 16, line 15 - page 17, line 7	10
L	WO 88 08671 A (WM. WRIGLEY JR. COMPANY) 17 November 1988 see page 5 - page 6	1,3,4

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 96/05468

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5294433 A	15-03-94	AU 3930493 A	18-11-93
		CN 1082400 A	23-02-94
		WO 9320815 A	28-10-93
		US 5364616 A	15-11-94
CA 2068366 A	11-11-92	NONE	
DE 2808160 A	30-08-79	NONE	
EP 151344 A	14-08-85	AU 3668684 A	08-08-85
		CA 1240875 A	23-08-88
		JP 60164438 A	27-08-85
		US 4753805 A	28-06-88
WO 8808671 A	17-11-88	US 4792453 A	20-12-88
		AU 612367 B	11-07-91
		AU 1721288 A	06-12-88
		CA 1329891 A	31-05-94
		DE 3886895 D	17-02-94
		DE 3886895 T	28-04-94
		EP 0314739 A	10-05-89
		FI 93689 B	15-02-95
		FI 93689 C	26-05-95
		JP 2500483 T	22-02-90